MC(JBW): Simple but Smart Monte Carlo Algorithm for Free Energy Simulations of Multiconformational Molecules

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ABSTRACT: Many of the most common molecular simulation methods, including Monte Carlo (MC) and molecular or stochastic dynamics (MD or SD), have significant difficulties in sampling the space of molecular potential energy surfaces characterized by multiple conformational minima and significant energy barriers. In such cases improved sampling can be obtained by special techniques that lower such barriers or somehow direct search steps toward different low energy regions of space. We recently described a hybrid MC/SD algorithm [MC(JBW)/SD] incorporating such a technique that directed MC moves of selected torsion and bond angles toward known low energy regions of conformational space. Exploration of other degrees of freedom was left to the SD part of the hybrid algorithm. In the work described here, we develop a related but simpler simulation algorithm that uses only MC to sample all degrees of freedom (e.g., stretch, bend, and torsion). We term this algorithm MC(JBW). Using simulations on various model potential energy surfaces and on simple molecular systems (*n*-pentane, *n*-butane, and cyclohexane), MC(JBW) is shown to generate ensembles of states that are indistinguishable from the canonical ensembles generated by classical Metropolis MC in the limit of very long simulations. We further demonstrate the utility of MC(JBW) by evaluating the room temperature free energy differences between conformers of various substituted cyclohexanes and the larger ring hydrocarbons cycloheptane, cyclooctane, cyclononane, and cyclodecane. The results compare favorably with available experimental data and results from previously reported MC(JBW)/SD conformational free energy calculations.
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Introduction

Converged molecular properties from free energy simulations can be obtained only extensive sampling of the potential energy surface of a system. Unfortunately, the two most commonly used methods in the field, molecular or stochastic dynamics (MD or SD) and Metropolis Monte Carlo (MMC), have difficulty in sampling all the low energy regions of conformational space when there are significant energy barriers (e.g., > 5 kcal/mol) between minima or when conformational space is large and sparsely populated.[1] In such cases significantly improved sampling can be obtained by various so-called *smart* simulation techniques, and several such procedures have been described in the literature.[2] While many of these methods have been shown to accelerate convergence with simple systems, none has been shown to provide a practical solution to sampling the potential energy surface of conformationally flexible organic molecules of contemporary complexity.

To address such problems, we developed and recently described a hybrid MC/dynamics simulation algorithm [MC(JBW)/SD] that included a smart MC procedure to accelerate conformational sampling.[3] This algorithm used the results of an initial conformational search to direct a smart MC procedure to jump repeatedly between diverse conformational states. We termed the MC part of this algorithm JBW for *jumping between wells*. JBW is related to previously described algorithms that use information about the potential energy surface to speed barrier crossings in double well systems[2l] and simple molecules.[2m,n] In MC(JBW)/SD the JBW operates by directing MC moves in the subset of the molecule's bond and torsion angles to preferentially sample diverse, low energy regions of the potential energy surface while SD varies all degrees of freedom to sample conformational space locally. Although we found MC(JBW)/SD to be much more efficient than classical methods for free energy simulations of conformationally flexible organic molecules, the complexity of the tightly integrated MC and SD algorithm is likely to limit its use by other workers.

In this work we describe a simple JBW-based Monte Carlo algorithm for simulations of multiconformational molecules. The new algorithm, termed MC(JBW), is a modification of the simple MMC[4] and it operates efficiently in all degrees of freedom. Here we compare its results with those from MC(JBW)/SD and classical MMC by free energy simulations of a range of flexible organic molecules.

MC(JBW) Algorithm

The MC(JBW) algorithm is closely related to part of the MC(JBW)/SD algorithm previously described.[3] Thus, it is a two-step procedure in which the low energy regions of a potential energy surface are first found (by a conformational search in the case of molecules) and then used to direct a modified MC procedure to jump repeatedly between them. The algorithm is based on Voter's modification[2n] of the standard MMC algorithm, and it replaces the traditional totally random moves with random moves modified by conformation-dependent but otherwise constant offsets (T_{ij} below). The algorithm operates as follows.

Step 1. Carry out a conformational search to find the set of low energy conformers; call these X_i. Evaluate the internal coordinate (Z matrix) transformations that interconvert all pairs (i, j) of the conformers in the X_i list; call these transformations T_{ij}.

Step 2. Pick an initial conformation; call this structure Y_0.

Step 3. Find the conformer on the X_i list that is closest to Y_0; call this conformer X_0.

Step 4. Randomly choose a conformer from the X_i list; call this conformer X_T.

Step 5. Apply transformation $T_{x_0 x_T}$ to structure Y_0 to generate structure Y_1.

Step 6. Apply small random variations to randomly chosen internal coordinates of Y_1 to generate the new trial structure Y_2.

Step 7. Verify that the resulting structure Y_2 is indeed closest to the intended trial structure X_T. If not, reject the step.

Step 8. Compare energies of Y_0 and Y_2, accepting Y_2 with a probability defined by Metropolis:[4]

$$p = \min\{1, \exp[-(EY_2 - EY_0)/kT]\}.$$

Step 9. Define the resulting structure as Y_0 and go back to step 3.

A significant difference between the above MC(JBW) algorithm and that used in our previous MC(JBW)/SD procedure is the addition of step 7.

This step isolates each conformational energy well (as defined by the X_i list) and solves the previously noted problem of ensemble dependence on the number of distinct conformers that are defined within a given conformational basin or family. Specifically, with certain model potentials having a broad energy basic made up of several minima separated by small barriers, we found that the generated ensemble was incorrect if more than one minimum from within that basin was included in the X_i list.[3] Although we could find no evidence that this problem had an impact on the ensembles generated by simulations of certain highly flexible molecules [e.g., on the populations of cyclononane's twist-chair-chair (TCC) and TCTC conformations that are very similar in structure and separated by an energy barrier of ~ 0.1 kcal/mol], we deal with the problem here by way of step 7 above. The basic problem is that when two conformers on the X_i list are very similar in structure (when the conformational energy well of a conformer is wide relative to its separation from another conformer in conformational space), jumps directed toward X_T may end up in some other well and the Y_2 energy used for the step 8 Metropolis test no longer refers as it should to the X_T well. Voter[2n] deals with this issue by simulating each well separately and not actually jumping from well to well. (He only records well to well transition probabilities.) Our step 7 accomplishes the same goal of forcing the algorithm to treat the energy wells around each conformational minimum (above as defined in the X_i list) as distinct and independent systems.

Validation Tests with Model Potentials

As part of a validation study for the MC(JBW) procedure, we carried out a range of simulations of a particle on various 1- and 2-dimensional model potential surfaces including those previously described.[3] As measures of the ensemble averages, we took the first two moments of the potential energy distribution (average and standard derivation) and the populations of the various wells in each potential. Due to the simplicity of the test potentials, we were able to obtain the correct results both by numerical integration (NI) using the trapezoid method and by MMC simulations. Our MMC and MC(JBW) simulations were initiated from arbitrary points on the 10-Å potential surfaces and all simulations were carried out at the temperature of 300 K. For MMC we used a maximum step size of 10 Å along all axes to force complete coverage of each surface. For MC(JBW) the conformers (X_i) of step 1 corresponded to the centers of the wells in the test potential and the transformation matrices (T_{ij}) consisted of simple translation vectors given by differences in the coordinates of the well centers. The step 6 randomization consisted of $0-(\pm)1$ Å translations along each axis.

We will not detail our MC(JBW) results on these previously described potentials[3] but simply state that all of our studies showed that the ensembles generated by MC(JBW) and MMC were indistinguishable as measured by the potential energy moments and well populations. However, one potential surface deserves special comment because it caused a problem in our previous MC(JBW)/SD simulations as discussed in the preceding section.[3] This system is a pseudo double well potential (Fig. 1) in which the broad, right-hand well actually consists of two wells (at ~ 3 and ~ 5 Å) separated by a very small energy barrier (0.01 kT at 4 Å). We previously asked whether the JBW procedure should take this system to be a two-well or three-well system: should the X_i conformational list have two or three (or more) entries? While it should not make any difference for a robust simulation algorithm, the JBW component of our previously described MC(JBW)/SD procedure had trouble with this system in that the ensembles generated varied depending on whether the system was defined as having two wells [Fig. 1, JBW(1)], three wells [JBW(2)], or four wells [JBW(3)].

With our new MC(JBW) algorithm incorporation of step 7 check of well identity, the situation is

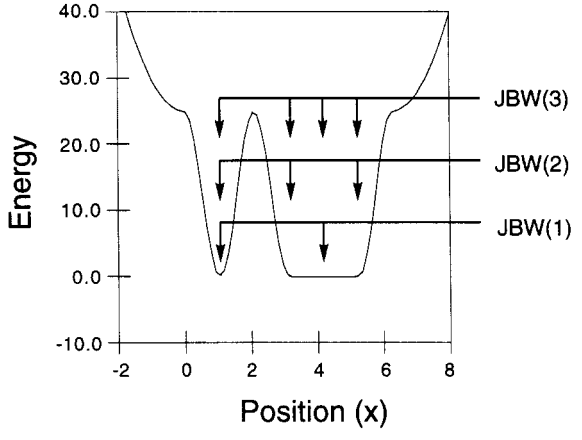

FIGURE 1. Multiple well test potential plotting energy (y axis) versus particle position (x axis).

TABLE I.
Comparison of Potential Energy (kJ / mol), Averages ([PE]), Standard Deviations (SD), and Well Populations with Figure 1 Potential from Various Simulation Methods.

			Exact Allocation Method			RMS Allocation Method		
	NI	MMC	JBW(1)	JBW(2)	JBW(3)	JBW(1)	JBW(2)	JBW(3)
⟨PE⟩	0.347	0.347	0.347	0.347	0.347	0.347	0.347	0.347
SD	1.154	1.154	1.155	1.154	1.155	1.153	1.154	1.155
Well 1	0.134	0.134	0.134	0.134	0.134	0.134	0.134	0.134
Well 2	0.866	0.866	0.886	0.886	0.886	0.886	0.886	0.886

much better as indicted in Table I. Thus, the potential energy moments and well populations are virtually identical by NI, classical MMC, and MC(JBW), regardless of whether the potential is considered to be a 2-, 3- or 4-well system. Figure 2 provides a more detailed comparison of the ensembles generated by MMC and MC(JBW) in the form of a histogram plot of the particle populations along the X axis in 0.2-Å bins. As the population histograms clearly show, all three MC(JBW) simulations generate ensembles that are indistinguishable from the correct ensemble generated by classical MMC.

In the MC(JBW) simulations on model potentials above, the potential energy surface was divided into conformational energy basins or wells based on the precise location of the energy barriers; assignment of the particle position to one of the members of the X_i list (step 3) was based on the division (termed the *exact allocation method*). While this simple method of conformational assignment is feasible for 2-dimensional surfaces, it is less easy to apply to the multidimensional energy surfaces of complex molecules. We therefore investigated an alternative, more general allocation scheme in which a particle or simulation structure is defined as belonging to the energy well that has the smallest root mean square (RMS) deviation from the corresponding minimum energy structure (the *RMS allocation method*). Ideally, the simulation procedure would not be sensitive to the details of the allocation procedure but give the same ensemble with either allocation method. The Figure 1 potential is a good test because, when viewed as a two-well system [JBW (1)], particle positions just the right of the first energy barrier are clearly in the basin of well 2 but are closer to minimum 1 by the RMS criterion. One might worry therefore that two different allocation schemes might give differing results. Therefore we carried

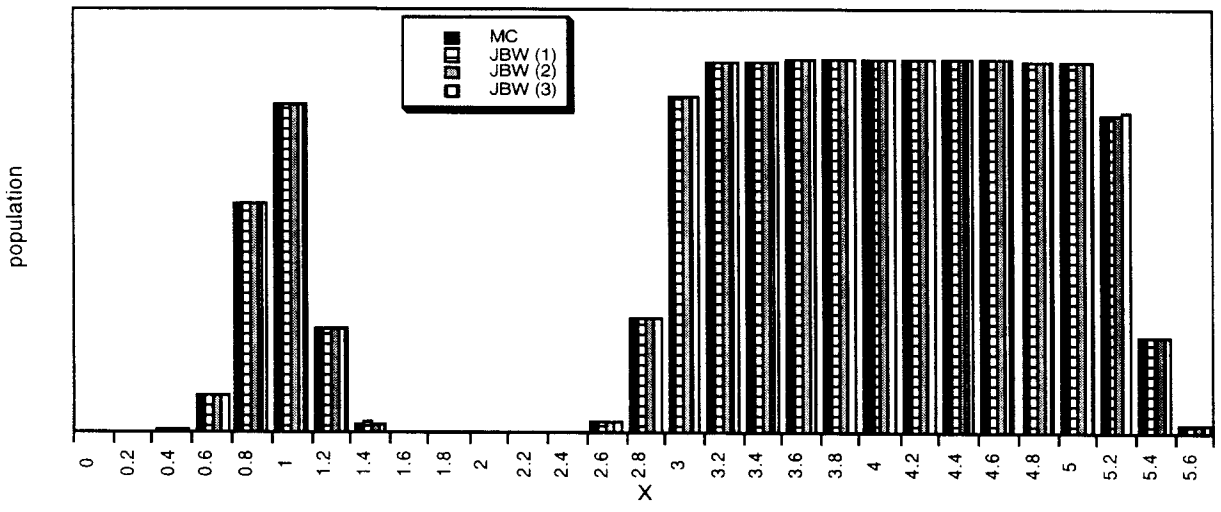

FIGURE 2. Comparison of particle position populations for Figure 1 potential from MMC and variious MC(JBW) simulations (see text).

out 10^9-step MC(JBW) simulations using the exact and RMS allocation methods for step 3. The results are given in Table I with all well populations defined by the exact allocation method for comparison. These results show that MC(JBW) generates ensembles with this potential that are indistinguishable from the correct ones given by NI or MMC, regardless of the allocation method or number of wells in the X_i list.

Validation Tests with Molecular Systems: *n*-Pentane, *n*-Butane, and Cyclohexane

To test the MC(JBW) algorithm on molecular systems, we implemented it in the MacroModel V5.5 distribution of our simulation program BatchMin[5] as follows.

In step 1 of the MC(JBW) algorithm, molecular conformations (i.e., members of the X_i list) are obtained by an internal coordinate SUMM conformational search,[6] although other search methods could also be used. We typically use all minimum energy conformers within 5 kcal/mol of the global minimum for the X_i list. For molecules having potential symmetry, these conformers include both members of enantiomeric conformational pairs and all possible molecular numbering systems. The transformation matrices (T_{ij}) consist of changes in the molecule's complete, nonredundant internal coordinates (defined by Z matrices including $n-1$ bond lengths, $n-2$ bond angles, and $n-3$ torsions where n is the number of atoms) that when applied to X_i will generate X_j.

In step 3 of the MC(JBW) algorithm, the conformational family of a given conformation is determined by an RMS comparison with the members of the X_i list in either Cartesian space (CRMS, after least squares superimposition) or in torsion space (TRMS, the preferred method).

In step 5 of the MC(JBW) algorithm, the transformation matrix is applied to structure Y_0 by first making the $T_{X_0X_T}$-defined changes to the Z matrix of Y_0 and then building structure Y_1 from those new internal coordinates. The Z matrix representation implicitly defines dependent ring closure bonds for any ring substructures. Because JBW moves transition from one low energy conformational region to another, ring closure bonds are not unreasonably distorted during moves. Thus, the algorithm works efficiently with both cyclic and acyclic molecules.

In step 6 of the MC(JBW) algorithm, a random subset of (typically) three Z matrix coordinates is chosen and randomized. The randomization limits we used are $\pm 0.0-0.1$ Å for bond lengths and $\pm 0.0-5.0°$ for bond and torsional angles.

To test the MC(JBW) algorithm, we carried out 5×10^8 step MMC and MC(JBW) simulations at 300 K with variations of all internal degrees of freedom on *n*-pentane (united atom), *n*-butane (all atom), and cyclohexane (all atom). To judge and compare the ensembles generated, we accumulated the first four moments of the potential energy distribution (mean, standard deviation, skew, and kurtosis)[7] and the conformational populations. Convergence was assessed by analyzing the populations of symmetrically equivalent conformations.

UNITED ATOM *n*-PENTANE

The results of our MMC and MC(JBW) simulations of (five particle) *n*-pentane using the united atom AMBER* force field[8] are given in Table II and suggest that both methods generate the same ensembles in the limit of long simulations. Convergence of these simulations was estimated by comparing populations within the symmetrically equivalent *ag* (ag^+, ag^-, g^+a; *a* is *anti* and *g* is *gauche*), g^+g^+ (g^{++}, g^-g^-) and g^+g^- (g^+g^- and g^-g^+), families and indicates that conformational populations are converged to 3 significant figures with the MMC and MC(JBW).

For this system we also investigated two alternative conformational RMS allocation schemes (step 3 of the JBW algorithm): one in Cartesian coordinates after least squares superimposition (CRMS) and the other in torsion angles (TRMS). As shown in Table II, both allocation methods lead to the same ensembles within the convergence-defined limits of our simulations. TRMS-based allocation seems to be a more natural choice for defining conformations with molecular systems and is therefore used throughout the rest of the work. Finally, in column 5 of Table II we given the results of our previous MC(JBW)/SD simulations *n*-pentane.[3] The published energy moment and population data from MC (JBW)/SD are very similar to those from MMC and MC(JBW) with the largest differences being found in conformational populations (*aa*, 41.0 vs. 42.1%; *ag*, 11.8 vs. 12.3%).

ALL ATOM *n*-BUTANE

The results of our MMC and MC(JBW) simulations of (14 particle) *n*-butane using the (all atom)

TABLE II.
United Atom *n*-Pentane.

	MC(JBW)			
	MMC	CRMS	TRMS	MC(JBW) / SD
⟨PE⟩	2.97	2.97	2.97	2.97
SD	1.37	1.37	1.37	1.37
SK	0.20	0.20	0.20	0.20
KU	0.26	0.26	0.26	0.26
Populations				
aa	0.421	0.421	0.421	0.410
ag^+	0.123	0.123	0.123	0.118
ag^-	0.123	0.123	0.123	0.118
g^+a	0.123	0.123	0.123	0.118
g^-a	0.123	0.123	0.123	0.118
g^+g^+	0.039	0.040	0.040	0.038
g^-g^-	0.040	0.040	0.040	0.038
g^+g^-	0.0041	0.0041	0.0041	0.0030
g^-g^+	0.0041	0.0041	0.0041	0.0029

The table is a comparison of ensemble average energies (⟨PE⟩; kcal / mol), standard deviations (SD), skews (SK), kurtoses (KU), and minima populations between 5×10^8 steps MMC, Cartesian RMS-MC(JBW) (CRMS), torsional RMS-MC(JBW) (TRMS), and 100-ns MC(JBW) / SD simulations at 300 K.

AMBER* force field are given in Table III. As is evident from the equal populations of the symmetrically equivalent g^+ and g^- conformers, both simulations are well converged. MC(JBW) is again found to generate an ensemble that is indistinguishable from that of classical MMC.

CYCLOHEXANE

MMC simulations [but not MC(JBW) ones, see below] have difficulties in sampling the potential energy surfaces of cyclic molecules because conformational interconversions require a concerted move of several internal degrees of freedom, an uncommon occurrence when the moves are random. Indeed, we found it impractical to use simple MMC to adequately interconvert the two symmetrically equivalent chair conformations of cyclohexane using standard molecular mechanics force fields.

TABLE III.
All Atom *n*-Butane.

	MMC	MC(JBW)
⟨PE⟩	12.511	12.516
SD	2.561	2.562
SK	0.110	0.110
KU	0.074	0.074
Populations		
a	0.535	0.535
g^+	0.233	0.232
g^-	0.233	0.232

The table is a comparison of ensemble average energies (⟨PE⟩; kcal / mol), standard deviations (SD), skews (SK), kurtoses (KU), and conformational populations between 5×10^8 step MMC and MC(JBW) simulations at 300 K.

TABLE IV.
All Atom Flexible Cyclohexane.

	MMC	MC(JBW)
⟨PE⟩	16.605	16.605
SD	2.914	2.913
SK	0.094	0.094
KU	0.055	0.055
Populations		
Chair 1	0.20	0.21
Chair 2	0.21	0.20
Twist-boat 1	0.10	0.10
Twist-boat 2	0.10	0.10
Twist-boat 3	0.10	0.10
Twist-boat 4	0.10	0.10
Twist-boat 5	0.10	0.10
Twist-boat 6	0.09	0.10

The table is a comparison of ensemble average energies (⟨PE⟩; kcal / mol), standard deviations (SD), skews (SK), kurtoses (KU), and minima populations between 5×10^8 step MMC and MC(JBW) simulations at 300 K.

To compare MC(JBW) with MMC results for cyclohexane, we modified the AMBER* force field to facilitate ring-flipping conformational changes by setting all torsional parameters to zero and by reducing the C—C stretch force constant from its original value of 310 to 31 kcal/mol-Å^2. These force field modifications reduced the chair (C)-twist boat (TB) steric energy difference from 5.8 to 0.7 kcal/mol and reduced to energy barrier for torsional rotations enough to allow frequent ring flips by MMC. The results of our MMC and MC(JBW) simulations of cyclohexane using the modified force field are given in Table IV. As before, the data indicate that both simulations are converged (virtually identical populations of the two equivalent C and six equivalent TB conformations) and that MMC and MC(JBW) generate the same conformational populations with the flexible cyclic molecule.

Conformational Populations and Free Energies of Typical Organic Molecules

Having demonstrated that 300 K MC(JBW) simulations give conformational populations and energy moments that are indistinguishable from those of the corresponding classical MMC simulations with *n*-pentane, *n*-butane, and (an unnaturally flexible model of) cyclohexane, we now apply MC(JBW) to the calculation of *in vacuo* conformational free energies of somewhat more complex, conformationally flexible organic molecules. The approach we use involves monitoring the populations of the various conformers of a molecular during a single, lengthy MC(JBW) simulation in which the conformers are frequently interconverted (i.e., are in rapid equilibrium). Conformational free energies then follow simply from $\Delta G = -RT \ln K_{eq}$. Given that such simulations produce converged, Boltzmann-weighted ensembles of conformational states, the energies evaluated by such a procedure will be the fully anharmonic, conformational free energies that are defined by the constitution of the molecule, the molecular mechanics force field, and the temperature.

This procedure assumes that the conformers are sampled with their correct statistical weights (i.e., that is the simulation is converged) and that it is always possible to determine in which conformation the system is. We establish convergence by investigating molecular systems having one or more elements of symmetry and by independently tabulating populations of symmetry-equivalent conformations. With respect to the conformational identity question, we compare structures from the MC(JBW) simulations with each of the known minimum energy conformers (X_i list) using a least squares superimposition in torsional coordinates (TRMS, except when otherwise noted). The X_i conformer having the smallest RMS deviation from the simulation structure is taken to define the conformation of that structure. All of our MC(JBW) simulations were run for 10^8 steps at 300 K. Below we compare these results to those of previously reported MC(JBW)/SD simulations[3] (using the same force field and temperature) and, when possible, to experimental data.

Our first MC(JBW) simulation addresses a basic conformational analysis problem, the free energy difference between the axial and equatorial conformations of methylcyclohexane (the so-called A value for methyl). Experimentally, the methyl A value is estimated from ^{13}C NMR measurements in $CFCl_3$—$CDCl_3$ solution at low temperature to be 1.63−1.82 kcal/mol at 300 K.[9] Our MC(JBW) simulations of methylcylohexane were run *in vacuo* using the MM2[10] and AMBER*[8] force fields (without the force field modifications described above for cyclohexane) and resulted in ~60,000 (all atom MM2) and ~150,000 (united atom AMBER*) interconversions between the two alternate chair forms. Such frequent interconversions are remarkable in comparison with the behavior of the real molecule; its 10 kcal/mol conformational barrier implies that conformer interconversion occurs only one every 3 μs[11] and makes simple MD or SD simulations of this system quite impractical. The A values obtained from our MC(JBW) simulations were 1.95 and 1.55 kcal/mol for MM2 and AMBER*, respectively, and are in good agreement with the experiment (1.63−1.82 kcal/mol) and with our previous MC(JBW)/SD simulations (1.99 and 1.51 kcal/mol for MM2 and AMBER*, respectively.[3]

Isopropylcyclohexane is generally similar in its conformational behavior to methylcyclohexane except that entropy favors the equatorial conformer in which the isopropyl substituent is more mobile than methyl. As a result, the A value of isopropyl exceeds that of methyl. Experimentally, the isopropyl A value is estimated from low temperature ^{13}C NMR measurements in $CFCl_2$—$CDCl_2$ solution to be 2.0−2.4 kcal/mol at 300 K.[9] Using the same method employed for methylcyclohexane above, our MC(JBW) simulation of isopropylcyclohexane using the MM2 force field gave a free

energy A value of 2.44 kcal/mol, once more in good agreement with the experiment and our previous MC(JBW)/SD results (2.6 kcal/mol).[3]

Finally we consider the conformational free energies of the cyclic hydrocarbons cycloheptane, cyclooctane, cyclononane, and cyclodecane on the MM2 potential surface at 300 K. To account for the effect of symmetry on entropy and to monitor convergence, conformers in the X_i list explicitly included enantiomers and all possible numbering systems: for example, the cycloheptane X_i list included 14 equivalent structures with the twist chair (TC) conformation and 14 with the boat (B) conformation. By monitoring the populations of equivalent conformations, we could readily judge the extent of simulation convergence. Thus, we found that the 14 equivalent TC conformers of cycloheptane were each populated to the extent of 6.2–7.5% while the 14 B conformers had populations of 0.04–0.06% in our 10^8-step simulations. Similar degrees of convergence were obtained for the other cycloalkanes. The results of our MC(JBW) simulations are summarized in Table V along with molecular mechanics steric energy differences (SE), SE corrected for differential entropies of mixing based on conformer degeneracy ($G_{300\text{K-MM}}$) and SE corrected for differential entropies of mixing and for the effect of rigid rotor, harmonic oscillator motion ($G_{300\text{K-Harmonic}}$). While the anharmonic conformational free energies ($G_{300\text{K}}$) from MC(JBW) simulation are qualitatively similar to the appropriately weighted molecular mechanics steric ener-

TABLE V.
Conformational Energies (kcal / mol) of Cyclic Hydrocarbons with MM2* Force Field.

Molecular	Conformation	SE[a]	$G_{300\text{K-MM}}$[b]	$G_{300\text{K-Harmonic}}$[c]	$G_{300\text{K-MC(JBW)}}$[d]	$G_{300\text{K-MC(JBW)/SD}}$[e]
Cycloheptane	TC[f]	0.0	0.0	0.0	**0.0**	0.0
	B[g]	3.15	3.15	1.66	**2.9**	2.8
Cyclooctane	BC[h]	0.0	0.0	0.0	**0.0**	0.0
	TCC[i]	0.97	1.38	0.86	**0.6**	0.7
	TBC[j]	1.66	1.66	1.47	**1.3**	1.3
	S4[k]	3.12	3.53	3.37	**3.4**	3.4
Cyclononane	TBC[l]	0.0	0.0	0.28	**0.4**	0.3
	m	0.75	0.10	0.0	**0.1**	0.1
	TCC[n]	0.77	0.12	0.11	**0.0**	0.0
	TCTC[o]	2.22	1.15	0.93	**0.9**	0.9
Cyclodecane	BCB[p]	0.0	0.0	0.04	**0.6**	0.4
	q	0.42	0.01	0.0	**0.0**	0.0
	r	1.12	0.71	0.73	**1.1**	0.9
	TCCC[s]	1.13	1.13	1.05	**1.3**	1.2
	TBCC[t]	1.53	0.70	0.66	**0.8**	0.8

[a] MM2 energy minimized, steric energy relative to global minimum.
[b] Molecular mechanics SE plus entropy of mixing effects from statistical weights at 300 K.
[c] $G_{300\text{-MM}}$ plus free energy effects calcualted at 300 K by normal mode analysis using the rigid rotor, hormonic oscillator approximation (symmetry number and zero point energy contributions not included).
[d] Conformational free energy from 10^8-step MC(JBW) simulation.
[e] Conformational free energy from 10-ns MC(JBW) / SD simulation in ref. 3.
[f] Torsion angles in degrees: −39, 88, −73, 55, −73, 88, −39.
[g] Torsion angles in degrees: 0, −70, 31, 57, −57, 31, 70.
[h] Torsion angles in degrees: −68, 68, −102, 44, 65, −65, −44, 102.
[i] Torsion angles in degrees: 85, −63, 85, −111, 85, −63, 85, −111.
[j] Torsion angles in degrees: 92, −49, −47, 117, −47, −49, 92, −89.
[k] Torsion angles in degrees: −36, −65, 36, 65, −36, −65, 36, 65.
[l] Torsion angles in degrees: 56, −125, 56, 56, −126, 56, 56, −125, 56.
[m] Torsion angles in degrees: 70, −67, −67, 70, 51, −103, 86, −103, 51.
[n] Torsion angles in degrees: −118, 73, −86, 122, −86, 73, −118, 65, 65.
[o] Torsion angles in degrees: −148, 90, −56, 89, −118, 103, −97, 47, 60.
[p] Torsion angles in degrees: 55, 66, −66, −55, 151, −55, −66, 66, 55, −151.
[q] Torsion angles in degrees: 151, −64, −58, 130, −58, −64, 151, −96, 54, −96.
[r] Torsion angles in degrees: −53, 138, −61, −77, 68, 68, −77, −61, 138, −53.
[s] Torsion angles in degrees: 145, −145, 84, −68, 84, −145, −145, −84, 68, −84.
[t] Torsion angles in degrees: 90, −156, 61, 72, −58, −52, 143, −135, 85, −62.

gies ($G_{300\text{-}MM}$), there are differences between the two-energies that amount to 0.2–0.8 kcal/mol. Thus, these studies confirm our previous findings that significant errors in conformational free energies can occur if conformational entropies are ignored or are estimated using the harmonic oscillator approximation (see Table V cycloheptane results for an extreme example).[3]

Also included in Table V are the results of previously reported MC(JBW)/SD simulations of these molecules, and these closely agree with the current MC(JBW) results. The cyclononane results are of particular interest because the TCC and TCTC conformers are very close in structure (largest torsion angle difference of 33°) and separated by a small ($\sim$0.1 kcal/mol) energy barrier on the MM2 or MM2* potential energy surfaces.[12] This situation is one where the MC(JBW) step 7 check discussed above might be expected to have a significant effect on the ensemble generated due to MC(JBW) jumps intended for TCC-like conformations ending up in the TCTC conformational basin and *vice versa*. Nevertheless, very similar conformational free energies were found at 300 K by MC(JBW) (with the step 7 check) and by MC(JBW)/SD (without step 7).

Conclusions

The above studies demonstrate that it is possible to devise a simple MMC-based simulation algorithm [MC(JBW)] that uses information about the positions of minima to efficiently sample the phase space of multiconformational organic molecules. In all of our tests including model potentials and flexible organic molecules, the MC(JBW) algorithm was found to generate ensembles that were indistinguishable from those of classical MMC within the limits of the convergence that could be attained. We have not tried to measure the efficiency of MC(JBW) relative to traditional methods such as MMC, MD, or SD because those methods cross typical conformational energy barriers so infrequently at 300 K that it would be impractical to make them converge on many of the systems described here. For example, the $\sim$10 kcal/mol barrier separating axially and equatorially substituted cyclohexanes would make it virtually impossible to use simple MMC or MD to generate a converged ensemble having the correct populations of both axial and equatorial states at room temperature.

Due to the accelerated conformational interconversion characteristics of MC(JBW), free energy simulations can now be carried out on a much wider array of flexible organic molecules than was possible previously. The main application of the algorithm will likely be to generate molecular ensembles for use in other calculations. These might include calculations of such ensemble-averaged observables as NMR coupling constants or nuclear Overhauser effects. The methodology should also be useful as an ensemble-generating technique for free energy calculations (e.g., free energy perturbation) on multiconformational molecules. The main limitations of the method are that it can be applied only to systems where the conformations are known or can be found (of course, that limitation applies to all other methods as well) and where solvation is treated as a continuum (e.g., the GB/SA water model[13]). These limitations notwithstanding, the MC(JBW) significantly extends the range of systems to which converged free energy simulation methodologies can be applied.

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